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EVIDENCE OF CHANGES IN CNS FUNCTION AT LOW-TO-MODERATE BLOOD LEAD LEVELS IN CHILDREN: A CHALLENGE TO CURRENTLY ACCEPTED THRESHOLD LIMITS

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16. ABSTRACT

What is the biological threshold of adverse central nervous system effect in children? The Centres for disease Control (1978) designated 30 µg/dl blood lead (PbB) and 50 µg/dl erythrocite protorphyrin as the upper "safe" limits of body burden, threshold values that are widely accepted in clinical practice today. However, considerable psychometric data (Meedleman et al, 1979; Yule et al 1981, Lansdown et al, Chapter 14) and electrophysiological data (Benignus et al, 1981; Landrigan et al, 1976; Otto et al, 1981; Seppalainen et al, 1972, 1975, 1980) from the peripheral and central nervous system of children and adults suggestive of lead related alterations of brain function at PbB levels below 30 µg/dl have been accumulating. Moreover, much of the data suggests a continuum of nervous system effects across a broad range of body lead burdens with no obvious threshold of effect (David et al, 1979; Landrigan et al, 1980). If the continuum model of lead effects is correct, then no arbitrary theshold limit of body burden can be considered absolutely safe in children. The objectives of this paper are to review recent electrophysiological data from our laboratory (Benignus et al, 1981; Otto et al, 1981, 1982) that are consistent with the continuum view; and to discuss some limitations in the interpretation of this data.

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What is the biological threshold of adverse central nervous system effect in children? The Centers for Disease Control (1978) designated 30 µg/dl blood lead (PbB) and 50 µg/dl erythrocite protoporphyrin as the upper "safe" limits of body burden, threshold values that are widely accepted in clinical practice today. However, considerable psychometric data (Needleman et al, 1979; Yule et al 1981, 1982) and electrophysiological data (Benignus et al, 1981; Landrigan et al, 1976; Otto et al, 1981; Seppalainen et al, 1972, 1975, 1980) from the peripheral and central nervous system of children and adults suggestive of lead-related alterations of brain function at PbB levels below 30 µg/dl have been accumulating. Moreover, much of the data suggests a continuum of nervous system effects across a broad range of body lead burdens with no obvious threshold of effect (David et al, 1979; Landrigan et al, 1980). If the continuum model of lead effects is correct, then no arbitrary threshold limit of body burden can be considered absolutely safe in children. The objectives of this paper are to review recent electrophysiological data from our laboratory (Benignus et al, 1981; Otto et al, 1981, 1982) that are consistent with the continuum view; and to discuss some limitations in the interpretation of this data.

METHODS

One hundred children (53 boys) aged 13 to 75 months were studied. These children came primarily from low-income Black families, a subset of the population that is known to be at increased risk for lead poisoning (Mahaffey et al., 1982). Parents of about half the children worked in a lead battery fabrication plant. Lead dust from work clothes was an

inadvertent source of contamination in some homes (Dolcourt et al, 1978). Peeling lead paint was the source of elevated PbB levels in other children.

This study was part of a comprehensive neurobehavioral evaluation that included a neurological examination; measurement of maternal and child IQ, language development, and motor activity and assessment of mother-child interaction in the home. Results of these assessments have been reported elsewhere (Milar et al, 1980, 1981).

Twenty-eight children (19 boys) from the original sample were re-evaluated two years later to determine if the observed relationship between slow brain potentials and body Pb burden persisted over time. Insufficient funds were available to re-assess all children from the original sample. Since children from battery factory families were considered to be at greatest risk, the follow-up study was limited to this group. The age range at follow-up was 35 to 95 months.

Blood lead (PbB) levels were measured from venipuncture samples obtained on the day of evaluation. Lead determinations were made in the Heavy Metals Laboratory of the University of North Carolina, a participant in the Centers for Disease Control Proficiency Testing Program. PbB levels were analyzed by flame atomic absorption spectrometry according to Delves (1970). PbB levels ranged from 6-55 µg/dl in the initial evaluation and 14-39 µg/dl in the follow-up study. Only three children had PbB levels above 30 µg/dl at re-evaluation. Demographic characteristics, PbB levels and IQs of children in the initial and follow-up samples are summarized in Table I.

Electrophysiological recording procedures have been described previously (Otto et al, 1981). In brief, EEG was recorded from the vertex, left and right parietal regions of the scalp referred to linked mastoids. Vertical eye movements were recorded for artifact editing. Trials with eye, muscle, or amplifier artifacts were eliminated from signal averages computed off-line. Analyses of EEG power spectra coherence and interhemispheric gain were computed from parietal leads as described by Benignus et al (1981).

In order to engage the attention of very young children during electrophysiological testing, cartoons were shown by 8 mm projector (initial study) or video tape recorder (follow-up). The basic testing paradigm was a passive sensory conditioning task in which a brief tone (conditioned stimulus) was paired with a short blackout of the cartoon (unconditioned stimulus). The interval between tone onset and video blackout was 1.5 seconds.

The conditioned electrophysiological response was computed as the mean EEG voltage during the one second interval preceding blackout. EEG was recorded during 35 trials in the initial study and 100 trials during follow-up. At least ten artifact-free trials were required for individual subject data to be included in slow wave (SW) analyses. Data from 65 children were used in the initial EEG spectrum analyses, from 41 children in the initial SW analysis, and from 28 children in the follow-up analysis. Subjects were rejected for medical, technical and behavioral problems. Only 13 children under 36 months of age satisfied criteria for inclusion in the SW analysis.

Stepwise multivariate procedures were used for statistical analysis. In order to maximize the power of a priori tests, SW analyses were limited

to one recording site (vertex). A regression model was chosen since the distributions of most variables were continuous. The first step was an overall test of the linear effects of demographic variables (age, sex, SES, and IQ). Linear, quadratic, and cubic effects of age and PbB were then tested using orthogonal polynomials.

RESULTS

No significant main effects of demographic variables were observed. Summary averages of slow cortical potentials recorded during initial and follow-up assessments are shown in Fig. 1. Regression analyses of slow wave (SW) voltage (Table II) revealed a significant age-by-PbB interaction in both the initial and follow-up samples. The nature of this relationship may be characterized as follows: SW voltage varied as a linear function of PbB, but the slope of this function changed with age. Fig. 2 illustrates this interaction. Results of the initial evaluation indicated that SW voltage in children under five years of age tended to be positive at PbB levels below 30 µg/dl, but to be negative at PbB levels above 30 µg/dl. Children over five years of age showed an opposite pattern: negative voltage at low PbB levels, but less negative or positive voltage at elevated PbB levels.

Results of the initial assessment presented in Table II differ slightly from the original report (Otto et al. 1981, Table III). A careful validation of all data used in the original analysis revealed a sizable error in the PbB value of one subject and several minor errors in ages and SES. The same multivariate regression analyses were rerun with corrected values. The use of corrected values reduced the error variance and increased the level of significance of several tests, although

the same age linear and PbB linear interaction was obtained. The main effect of PbB, which was only marginal in the original analysis ($p = .08$), reached significance in the re-analysis ($p = .038$).

During the initial assessment, 35 sensory conditioning trials were recorded from each subject. After editing the data for artifacts resulting from eye or body movement, too few trials remained for meaningful assessment of temporal changes during conditioning. In the follow-up evaluation, 100 trials were recorded from each child to permit a limited analysis of temporal changes. Individual averages of trials 1-40 and 41-100 were constructed to compare SW voltage during early and late conditioning. This asymmetrical breakdown of trials was necessitated to obtain approximately equal numbers of early and late trials since more artifact problems occurred during late trials. The middle and bottom rows of Fig 1 show summary averages of early and late trials, respectively. The voltage of early and late trials was inversely correlated ($r = -.46$, $p < .02$), suggestive of a polarity inversion during conditioning. This apparent inversion between early and late trials accounts in part for differences in the slopes of age functions for initial and follow-up data depicted in Fig. 2.

The effects of age and PbB on EEG power spectra and hemispheric laterality were also explored in the initial and follow-up assessments. Methods and results for the initial spectrum analyses are described in Benignus et al. (1981). No significant effects of PbB on power spectra or coherence measures were observed, although the relative amplitude of synchronized EEG between left and right hemispheres (gain spectra) increased relative to PbB levels. A significant cubic trend for gain

between the left and right parietal lobes was found as shown in Fig. 3. This effect was observed in all frequency bands (δ, θ, α, and β) at the time of the initial assessment, but no significant difference associated with PbB was found at follow-up.

DISCUSSION

This study offers provocative evidence of altered central nervous system function at blood lead levels below 30 µg/dl, the threshold above which children are presently considered to have an elevated body burden (Centers for Disease Control, 1978). SW voltage recorded from the scalp of young children during sensory conditioning varied as a linear function of PbB within an observed range of six to 55 µg/dl. The slope of this function, moreover, varied systematically with age. When a subset of the children was retested two years later, the same linear relationship of SW voltage, age and PbB was observed. EEG spectrum gain, an orthogonal measure of CNS function, was also found to vary as a function of PbB during the initial evaluation, although this measure did not vary significantly with PbB in the follow-up analysis. These data imply (1) that there is no clearly defined PbB threshold below which SW voltage is unchanged; and (2) that the altered brain wave patterns associated with asymptomatic body Pb burdens in young children persist for at least two years, despite a substantial reduction of the mean PbB level during the test-retest interval.

These data are consistent with a continuum model of lead neurotoxicity--i.e., that CNS deficits are proportional to body lead burden. According to the continuum model, CNS function is affected in a graded manner across the entire range of exposure -- i.e., there is no absolutely safe

criterion level of lead burden below which the developing nervous system will be unharmed. Evidence has been accumulating over the past four decades of the untoward sequelae of early asymptomatic lead exposure (see reviews by USEPA 1977, Rutter 1980, Bornschein et al. 1980). Mental retardation, minimal brain dysfunction attention-deficit disorders, and a variety of subtle learning disorders have been linked with exposure levels that do not produce overt symptoms of Pb poisoning and that are unlikely to be detected. Evidence of IQ and/or attentional deficits in children at PbB levels below 40 µg/dl have been reported by Needleman et al, 1979), Winneke et al (1982 a,b) and Yule (1981, 1982), although a variety of methodological questions have been raised (e.g., Ennhart et al, 1981) that cloud the interpretation of these data. These problems include the use of PbB measures as an index of body lead burden, extrapolation from tooth-Pb to blood-Pb measures, and possible confounding effects of other variables such as socioeconomic status, parental IQ, and child-rearing practices. Despite these problems, the aggregate of data from recent neurobehaviroal studies suggests that lead absorption in children produces a continuum of CNS impairments of increasing severity relative to the amount of Pb absorbed.

Failure of previous studies to demonstrate a linear relationship between PbB and neurobehavioral outcome may be the consequence of using statistical analyses that are relatively insensitive for evaluating the effects of continuous variables such as toxicant body burdens. In the present study a regression model was chosen because the distributions of critical variables (age, PbB, and EEG measures) were continuous. Any arbitrary grouping of data (such as 6-30 and 31-55 µg/dl PbB), as required

in a traditional analysis of variance, results in a loss of information. For instance, any EEG changes that might be present within a specific exposure group (e.g. 6-30 µg/dl) would be obscured by averaging all data within that group. If this grouping had been used in the present study and a significant difference had been observed between the "elevated PbB" and "normal PbB" groups, our conclusions might have been quite different. In all likelihood we would have interpreted our data in support of the prevailing view that PbB levels above 30 µg/dl are associated with increased prevalence of CNS abnormalities. The statistical model chosen thus has profound implications for the conclusions drawn from a particular data set. In particular, the ANOVA model tends to suggest an arbitrary "threshold" view of toxicant effects based on the comparison of discrete means, while the linear regression model tends to suggest a "continuum" view based on the utilization of a continuous range of exposure values.

Although the regression model permits a more efficient use of available data relative to the ANOVA model, limitations in the interpretation of results should be noted. Demonstration of a linear relationship in the absence of higher order effects is a case in point. For example, we observed a significant *linear* relationship of SW voltage and PbB within an observed range of six to 55 µg/dl. *However, we cannot arbitrarily pick the lower limit or any other value within the observed exposure range and conclude that a significant impairment exists at or below that point.* In order to identify a "threshold point" within the exposure continuum, a discontinuity (or inflection point) must be demonstrated. *A linear relationship over the observed range implies no such inflection point.* Tests for quadratic and cubic trends were, in fact, made (Table II) to

look for such inflection points. No significant higher order effect was found in the SW voltage analysis, although a cubic relationship of EEG spectrum gain and PbB was observed (Benignus et al. 1981). The prominent inflection point in this cubic function provided the basis for concluding that CNS effects of Pb exposure were observed below 15 µg/dl.

Finally, we would like to reiterate several other caveats in the interpretation of our data (Otto et al 1981, p 237-8):

> The use of blood lead level as an index of body burden is problematic. PbB level is an accurate measure of the amount of Pb circulating in the body at the time of sampling, but an isolated observation reveals little about the exposure history of the individual. A high value could reflect an uncharacteristic, episodic elevation in PbB level, while a low value could belie dangerously high exposures at an earlier (and extremely vulnerable) period of development. If PbB values obtained in the present sample were systematically low across the entire range of observations, a fixed error would be present in the predictor model and CNS effects would be attributed to artificially low body Pb burdens. Alternatively, if random sampling errors were encountered in PbB measures - a more likely possibility - the variance would presumably increase relative to the amount of error. That is, a systematic underestimate of PbB levels would tend to yield a nonconservative error, while random PbB fluctuations would tend to produce a conservative error.
>
> Another caveat concerns the nature of the measures. The paradigms used are experimental, normative data for young children do not exist, and the lack of concurrent behavioral measures limits the assessment of functional significance. Therefore, the present data must be considered preliminary until the results have been replicated.

In summary, we have observed statistically significant changes in two different parameters of CNS function (slow wave voltage and EEG gain spectra) within a range of low-to-moderate blood lead levels (6 to 55 µg/dl) in young children. The SW voltage change appears to persist for at least two years despite a substantial decrease in PbB levels. These results challenge the widely-accepted view that 30 µg/dl is a "safe" threshold below which no adverse effects will occur in

children. On the other hand, the limitations of PbB as an index of body burden and the experimental nature of the CNS measures employed must be clearly understood. Efforts to replicate and validate these findings in an independent sample are in progress.

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TABLE I. Demographic characteristics of initial and two-year follow-up samples

A. INITIAL EVALUATION SAMPLE (N = 75)*

	AGE IN MONTHS			
	13 - 35	36 - 59	60 - 75	SAMPLE MEAN (STANDARD ERROR)
N (MALE)	35 (19)	31 (17)	9 (2)	
PbB	29.8	28.5	27.8	29.0 (1.6)
IQ	89.2	79.7	90.8	85.5 (1.7)
SES	69.0	67.3	54.8	66.7 (1.5)

B. TWO-YEAR FOLLOW-UP SAMPLE (N = 28)

	AGE IN MONTHS		
	35 - 66	67 - 95	SAMPLE MEAN (STANDARD ERROR)
N (MALE)	16 (11)	12 (8)	
Original PbB	31.4	33.8	32.5 (2.4)
Follow-up PbB	21.5	20.5	21.1 (1.4)
Original IQ	90.1	83.4	87.1 (2.5)
Follow-up IQ	80.5	85.7	82.8 (1.8)
SES	67.3	62.7	65.2 (1.5)

abbreviations: N = sample size; PbB = blood lead level; IQ = intelligence quotient; SES = socio-economic status

*Subjects used in EEG spectra and/or slow wave analyses.

TABLE II. Results of multivariate regression analyses of slow wave voltage for initial and two-year follow-up assessments

Source	df (num, den)	F	P
Initial assessment			
Demographics	3, 37	2.32	.10
Age	3, 37	0.39	.76
PbB	3, 37	3.11	.038
linear	1, 37	5.51	.025
quadratic	1, 37	3.21	.09
cubic	1, 37	0.07	.79
Age x PbB	4, 35	5.40	.0018
linear x linear	1, 35	17.03	.0003
linear x quadratic	1, 35	0.23	.64
quadratic x linear	1, 35	0.32	.58
quadratic x quadratic	1, 35	0.81	.38
Follow-up assessment			
Overall test	6, 24	3.30	.009
All trials (1-100)			
Age	1, 24	0.36	.56
Mean PbB*	1, 24	7.16	.014
Age x Mean PbB	1, 24	2.66	.12
Early trials (1-40)			
Age	1, 24	0.48	.50
Mean PbB*	1, 24	0.15	.71
Age x Mean PbB	1, 24	0.35	.56
Late trials (41-100)			
Age	1, 24	2.65	.12
Mean PbB*	1, 24	6.61	.017
Age x Mean PbB	1, 24	7.22	.013

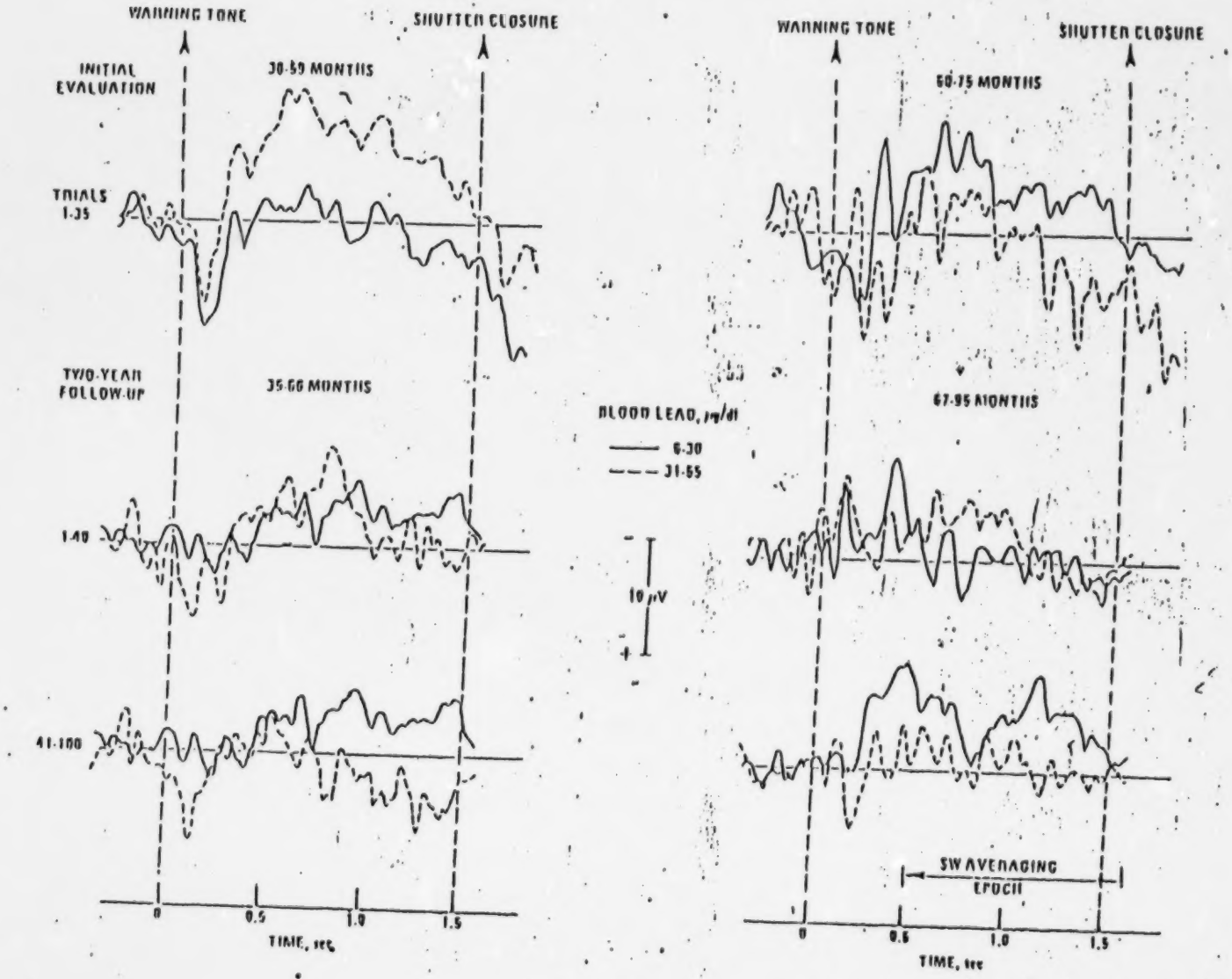
*Mean PbB was calculated for each child as the average value of initial and follow-up PbB values [(PbB1 + PbB2)/2]. This value provides a crude estimate of the mean body burden during the period between the initial and follow-up assessments.

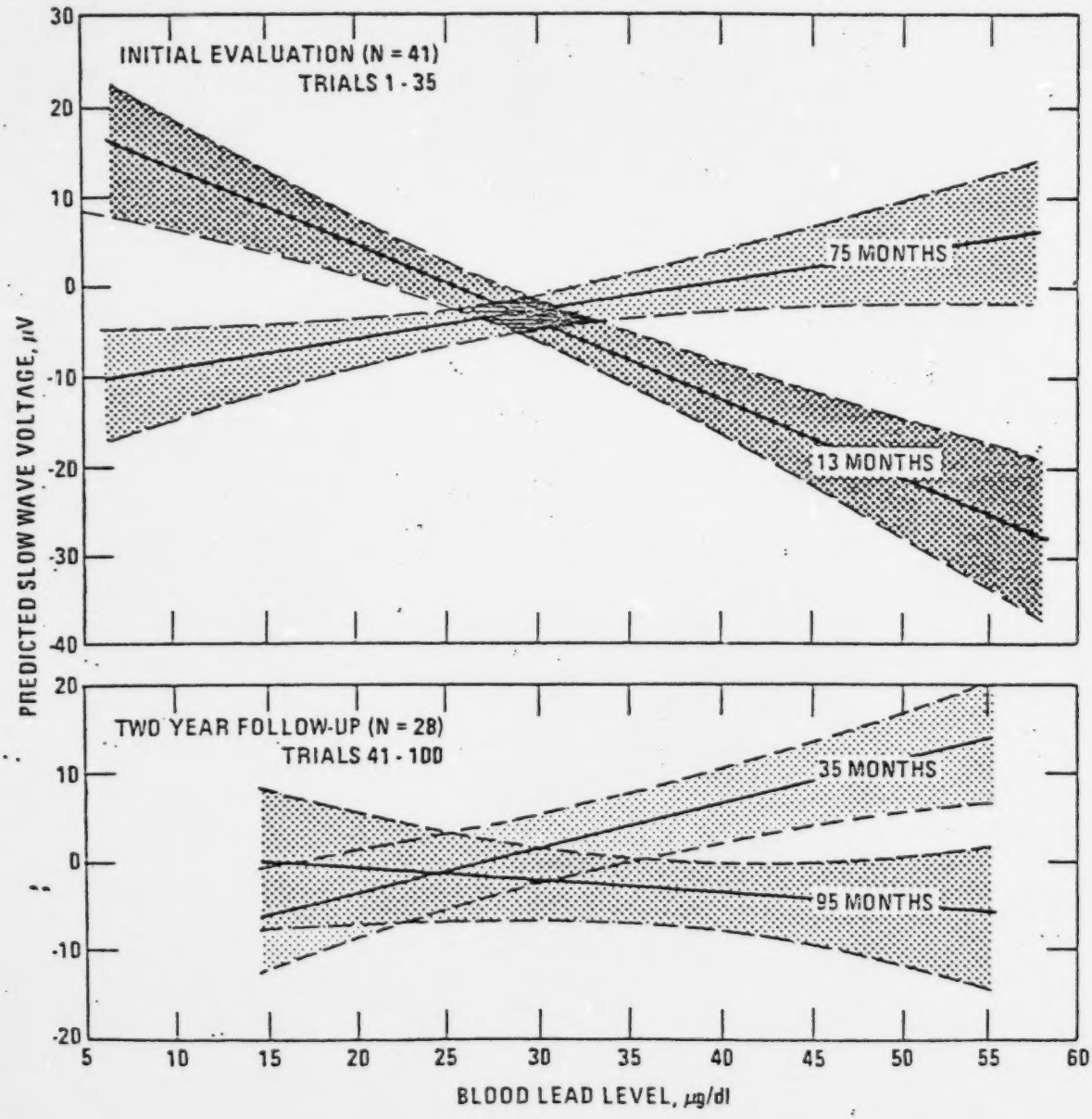
FIGURE LEGENDS

Fig. 1 Summary averages of slow cortical potentials recorded during sensory conditioning in children with elevated body lead burden. Children have been arbitrarily divided into younger (left column) and older (right column) age groups at blood lead levels above (dashed line) and below (solid line) 30 µg/dl. Averages in the top row were recorded from 41 children during the initial evaluation. Averages in the bottom two rows were recorded from 28 children two years later. Temporal changes in slow wave voltage during early (middle row) and late (bottom row) trials are also shown.

Fig. 2 Predicted slow wave voltage and 95% confidence bounds as a function of original blood lead levels for children at the extreme age ranges represented in the initial evaluation (upper box) and the follow-up evaluation (lower box). These plots depict the linear interaction of PbB and age.

Fig. 3 Estimated cubic trend line and 95% confidence bounds for EEG spectra gain between left and right hemispheres (P3 and P4) in the δ band as a function of blood lead (PbB) level. Age was held at a mean value of 36.8 months. (Reprinted from Benignus et al., 1981, p 245)


WARNING TONE
SHUTTER CLOSURE
INITIAL EVALUATION
30-59 MONTHS
TRIALS 1-35
TWO-YEAR FOLLOW-UP
35-66 MONTHS
1-40
41-100
0
0.5
1.0
1.5
TIME, sec
BLOOD LEAD, µg/dl
6-30
31-55
10 µV
WARNING TONE
SHUTTER CLOSURE
60-75 MONTHS
67-95 MONTHS
SW AVERAGING EPOCH
0
0.5
1.0
1.5
TIME, sec


INITIAL EVALUATION (N = 41)
TRIALS 1 - 35
75 MONTHS
13 MONTHS
TWO YEAR FOLLOW-UP (N = 28)
TRIALS 41 - 100
35 MONTHS
95 MONTHS
PREDICTED SLOW WAVE VOLTAGE, μV
BLOOD LEAD LEVEL, μg/dl
30
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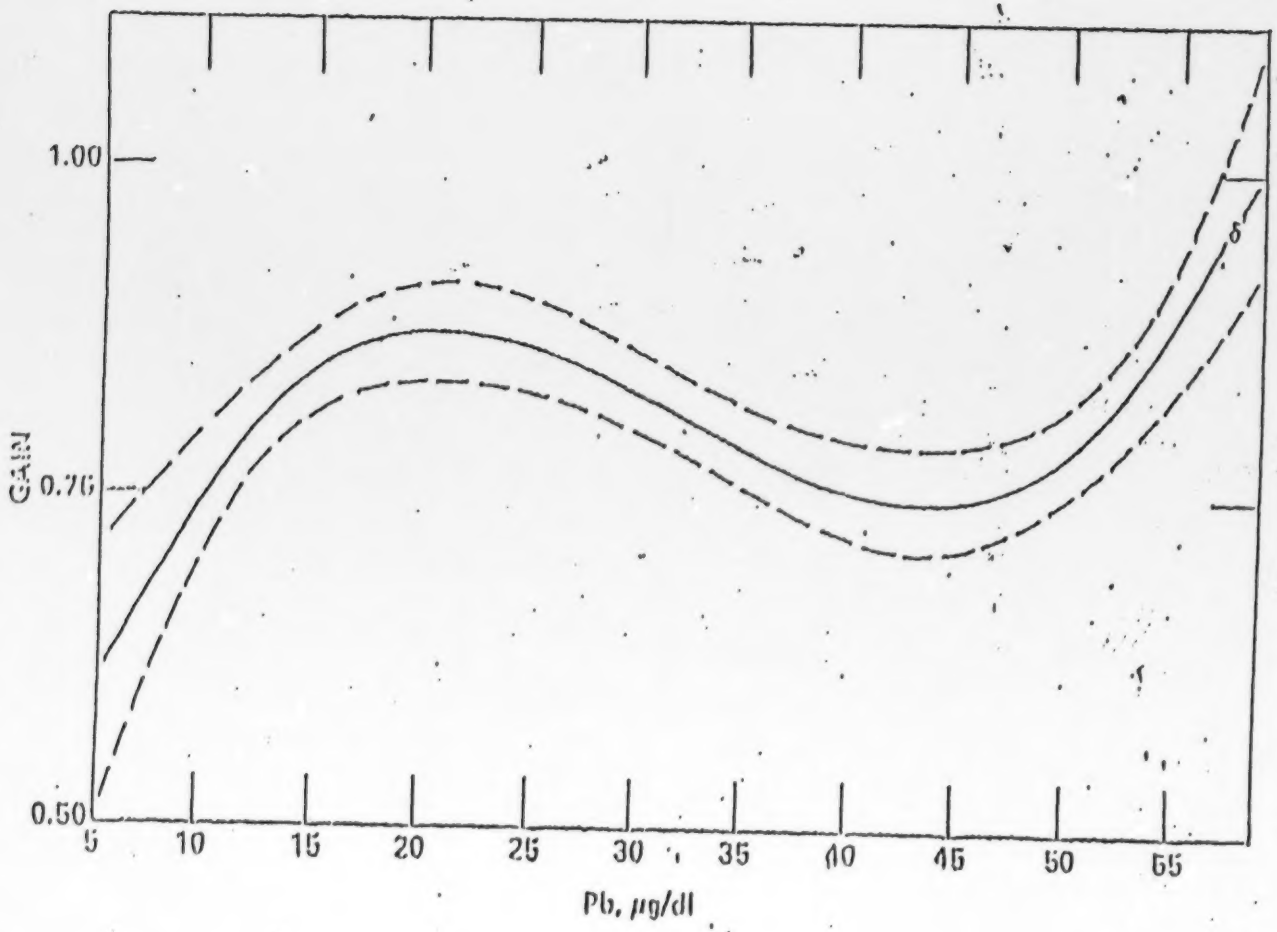
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